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Use of serum osmolality as a risk marker in patients with coronary artery disease: A cross-sectional, case-control study

Heart health and osmolality

Elif Seda Topuzoğlu[1], Turgut Karabağ[2]
[1] Department of Family Medicine, Yazlık Family Health Center, Düzce
[2] Department of Family Medicine, Health Sciences University, Istanbul Training and Research Hospital, Istanbul, Turkey

Abstract
Aim: Cardiovascular diseases are the primary cause of mortality and morbidity from non- communicable diseases. The purpose of this study is to examine the role of serum osmolality level for coronary artery disease.
Material and Methods: A cross-sectional case-control study was conducted between July 2019 and January 2020. It included 113 patients aged 35 years older with coronary angiography indication. Eighteen questions were asked to evaluate the sociodemographic characteristics. The patients were divided into two groups: critical coronary artery disease patients (Group 1) and normal coronary artery patients (Group 2). the Syntax and Gensini scores were used to calculate the severity and prevalence of the disease. The venous blood of the participants determined the serum osmolality value.
Results: The median age of patients in Group 1 was 58 (min-max: 37-88) years and 53.5 (min-max: 37-82) years in Group 2. Male sex (p=0.003), age (p=0.02), smoking status (p=0.004), waist-hip ratio (p=0.001), and heart rate (p=0.024) variables in Group 1 were significantly higher than in Group 2. There was no statistical difference between groups in terms of mean osmolality values (p=0.19). Osmolality findings were compared; while Gensini score was statistically significant in Group 1 (p=0.04), the Syntax score was not (p= 0.24). In the correlation analysis of age and osmolality findings with Gensini and Syntax Scores in Group 1, the age variable did not expressively differ. Osmolality increased significantly with the Gensini Score (p= 0.04) and had a weak correlation (r = -0.24). There was no increase (p = 0.24) with the osmolality Syntax Score, and weak correlation (r = - 0.14) was observed.
Discussion: As a result of the study, no statistical difference was found between the two groups in terms of serum osmolality levels.

Keywords
Coronary Artery Disease, Serum Osmolality Level, Gensini Score, Syntax Score

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Corresponding Author: Elif Seda Topuzoğlu, Yazlık Family Health Center, 50th ASM, Düzce, Turkey.
E-mail: sedatopuzoglu8@gmail.com P: +90 506 734 11 90
Corresponding Author ORCID ID: https://orcid.org/0000-0002-9149-7133

Introduction

Cardiovascular diseases (CVD) are the prominent cause of morbidity and mortality from non-communicable diseases in the world [1]. Therefore, easy identification of CVD risks and health protection are critical for primary care health services, one of the most important tasks of which is preventive medicine. Atherosclerosis coronary artery disease (CVD) is the most common cardiovascular disease. The pathogenesis of atherosclerosis is a response to vascular damage. The vascular endothelium is affected by blood flow abnormalities, which are influenced by different risk factors. The viscoelastic structure of the blood flow is important in this process, which depends on the corpuscular and biochemical components of the blood [2,3]. Many CVD risk factors have been identified, but they are basically divided into two groups: modifiable and non-modifiable. Non-modifiable risk factors are as follows: family history, sex, and age. Modifiable risk factors include smoking, diabetes mellitus, hypertension, dyslipidemia, sedentary life, and obesity [4].

Some studies determined that hyperosmolality initiates inflammation and atherosclerosis, causing morbidity and mortality [5,6]. Other studies, proved that hematological parameters such as plasma viscosity, hematocrit, and hemoglobin level are associated with the incidence of CVD [7,8]. Measurement of serum osmolality is a simple and cost-effective method, and examining its usability is important, to determine the risk at the beginning of the atherosclerotic process and to prevent it early by taking preventive measures. The purpose of this study is to examine the correlation between serum osmolality and CVD and to assess its usability for risk models.

Material and Methods

This cross-sectional case-Control study was conducted with people aged 35 years and older, who applied to the Cardiology Polyclinic and Emergency of Health Sciences University Istanbul Training and Research Hospital between July 2019 and January 2020 with any complaint and were found to have an indication for coronary angiography. The population consisted of 113 participants. Participation in the study was voluntary, and the participants were first informed about the study and their verbal consent was obtained. Among the participants, 39 were female and 74 were male, with a median age of 55 years.

Following patients were excluded from the study: patients with chronic renal failure, diabetes mellitus, connective tissue disease, malignancy, active infection, heart and/or liver failure, pregnant and lactating women, people who have undergone coronary artery bypass surgery, those who apply to the hospital with acute ST-Elevated Myocardial Infarction, use steroids, have a history of alcohol use in the last 24 hours, persons with fever, acute blood loss and signs of dehydration, patients using antihypertensives that affect electrolyte levels, patients with poor cooperation and orientation.

The study began after obtaining approval from the Ethics Committee of Health Sciences University Istanbul Training and Research Hospital dated 28/06/2019 and numbered 1892. The patients filled out a questionnaire asking age, sex, smoking status, hypertension, diabetes mellitus, renal failure, dyslipidemia, coronary artery disease, family history and medications. Systemic examination was performed before coronary angiography. Systolic and diastolic blood pressure, heart rate, body weight, height, hip, and waist circumference of the patients were measured with a tape measure (cm) and recorded. Weight measurements were made with the same scales. Morning venous blood samples were taken from all study patients after an overnight (at least 8 hours) fasting, and hemogram, pre-prandial blood glucose (PBG), urea, creatinine, AST, ALT, total cholesterol, HDL, LDL, TG, sodium, potassium, calcium levels of patients were measured afterwards. Plasma Osmolality was calculated using these values by the formula: (mOsm/kg) = (2xNa) + (Glucose/18) + (BUN/2.8).

Coronary angiography was performed, and for the assessment, >50% narrowing of the lumen in the main artery or its lateral branch was considered as critical stenosis. The coronary angiography images were examined by two cardiologists who were uninformed about the physical examination findings and complaints of the patients. Two cardiologists decided the level of narrowing in the coronary arteries. The patients were divided into two groups: critical coronary artery disease (stenosis greater than 50%-Group 1) and normal coronary artery disease (stenosis less than 10%-Group 2). Persons with 10%-50% stenosis detected by angiography were not included in the study.

Gensini Scoring

It determined the prevalence of coronary artery disease and to assess the atherosclerotic plaque burden. Since all lesions evaluated in the scoring system, the patient's total atherosclerotic plaque load can be calculated [9].

Syntax Scoring

The score determining the prevalence and severity of coronary artery disease, assesses the number of lesions, their functional significance, location, and complexity [10]. The Syntax score focuses on coronary vessel anatomy. This scoring system was prepared for the study named "Syntax", which was planned to determine the most appropriate treatment strategy for patients with three-vessel and/or left main coronary artery lesions.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS 25.0 IBM Statistics for MAC, Version 25.0) version 25.0 statistical package program was used to obtain the data. Controls and analyzes of the data were performed with the same program. The Kolmogorov-Smirnov test was used to examine the compatibility of numerical type features with a normal distribution. Descriptive statistics for numerical variables were expressed as median, and descriptive statistics for categorical data were expressed as numbers and percentages. The independent T-test compared two independent groups when the numerical variables were normally distributed, and with the Mann-Whitney U test when they were not. For quantitative variables, for more than two independent groups, the one-way ANOVA test was used when the assumptions were met, and the Kruskal-Wallis test was used when they were not. The Pearson correlation test analyzed the pairwise correlations of the variables if the assumptions were met, and the Spearman Rho correlation test if they were not. The results were evaluated at a 95% confidence interval, and $p<0.05$ was accepted as significant.

Results

The study included 113 volunteers; of these, 39 were female and 74 were male. In 71 patients, stenosis of more than 50% was detected in their coronary angiography. Coronary artery stenosis rate in 42 people was below 10%. The groups were divided into 2 groups as >50% stenosis (Group 1) and normal coronary artery (Group 2) to compare the data. Socio-demographic characteristics are presented in Table 1). The distribution of laboratory measurements is shown in Table 2. Correlation analysis was performed using Gensini and Syntax Scoring of serum osmolarity and age (Table 3).

Group 1 consisted of 16 female and 55 male participants, and 23 female and 19 male participants were included in Group 2. A statistically significant difference was found between the groups in terms of gender (p = 0.003). In the study, the mean age in Group 1 was 58.45 ± 10.89 years, and the mean age in Group 2 was 53.57 ± 10.11 years, and the age difference between the groups was statistically significant (p = 0.02). There were 41 smokers and 30 non- smokers in Group 1, and 13 smokers and 29 non-smokers in Group 2, and a statistically significant difference was found (p = 0.004). The mean Waist/Hip Ratio was 0.94 ± 0.051 for Group 1, and 0.90 ± 0.076 for Group 2, being statistically significant (p = 0.001). The mean heart rate in Group 1 was 94.7 ± 13.6, in Group 2 it was 86.7 ± 23.5, and a statistically significant difference was found (p = 0.024).

Table 1. Socio-Demographical Characteristics of Group 1 and Group 2 Participants

Stenosis Rate Detected by Coronary Angiography	Group 1 >50% stenosis (n = 71)	Group 2 <10% stenosis (n = 42)	p
Sex			
Female	16 (22.5)	23 (54.7)	0.003*
Male	55 (75.5)	19 (45.3)	
Age (year)	58.4 ± 10.8	53.5 ± 10.1	0.02*
HL (n)			
Yes	20 (28.2)	9 (21.4)	0.43
No	51 (71.8)	33 (78.6)	
CAD (n)			
Yes	1(7)	1 (2.4)	0.084
No	66 (93)	41 (97.6)	
Smoking (n)			
Yes	41 (57.7)	13 (30.9)	0.004*
No	30 (42.3)	29 (69.1)	
Family History			
Yes	28 (39.4)	19 (45.2)	0.54
No	43 (60.6)	23 (54.8)	
MS (n, %)			
Yes	36 (65.5)	19 (34.5)	0.57
No	35 (60.3)	23 (39.7)	
BMI (kg/m²)	71 (100) 28.02 ± 5.50	42 (100) 30.0 ± 5.45	0.067
Waist/hip ratio	0.94 ± 0.051	0.90 ± 0.076	<0.001
Systolic blood pressure (mmHg)	135.0 ± 20.7	137.0 ± 19.2	0.61
Diastolic blood pressure (mmHg)	80.2 ± 10.7	82.3 ± 15.6	0.39
Heart Rate	94.7 ± 13.6	86.7 ± 23.5	0.024*

p*< 0.05 statistically significant, HL: Hyperlipidemia, MS: Metabolic Syndrome

The comparison of laboratory values of Group 1 and Group 2 was as follows: preprandial blood glucose (106.52 ± 22.61 mg/dl vs. 97.23 ± 15.93 mg/dl; p = 0.02);

creatinine (0.78 ± 0.22 mg/dl vs. 0.68 ± 0.14 mg/dl; p = 0.01); total cholesterol (208.23 ± 65.07 mg/dl vs. 181.62 ± 42.77 mg/dl; p = 0.02); triglyceride values were significantly higher in Group 1 compared to Group 2 (162.12 ± 87.14 mg/dl vs. 124.69 ± 71.47 mg/dl; p = 0.02), while Sodium values were statistically significantly higher in Group 2 than in Group 1 (138.87 ± 2.34 mg/dl vs.139.92 ± 1.73 mg/dl, p = 0.01).

Serum osmolality levels of Group 1 (with stenosis over 50%) and Group 2 (with stenosis below 10%) were 289.52 ± 5.21 mOsm/kg and 290.77 ± 4.31 mOsm/kg respectively. There was no statistically significant difference between Group 1 and Group 2 in terms of the calculated mean serum osmolality levels (p = 0.19)

While the age variable was not significantly different to the Gensini and Syntax scores, osmolality was observed to increase significantly with the Gensini score and form a weak correlation, while it did not create a significant increase with the Syntax score, but still had a weak correlation.

Table 2. Laboratory Measurement Values of Group 1 and Group 2

	Group 1 (n = 71)	Cr value that is higher (n = 42)	P
PBG** (mg/dl)	106.5 ± 22.6	97.23 ± 15.93	0.02*
UREA (mg/dl)	34.8 ± 14.1	33.54 ± 10.78	0.60
BUN*** (mg/dl)	16.2 ± 6.6	18.70 ± 20.43	0.34
Creatinine (mg/dl)	0.78 ± 0.22	0.68 ± 0.14	0.01*
Total Cholesterol (mg/dl)	208.2 ± 65.0	181.6 ± 42.7	0.02*
TG (mg/dl)	162.1 ± 87.1	124.6 ± 71.4	0.02*
HDL (mg/dl)	43.7 ± 10.3	43.6 ± 10.6	0.95
LDL (mg/dl)	131.1 ± 51.6	120.1 ± 56.7	0.95
NA (mEq/L)	138.8 ± 2.3	139.9 ± 1.7	0.01*
K (mEq/L)	4.2 ± 0.4	4.1 ± 0.4	0.42

P*< 0.05 statistically significant, PBG**: Preprandial Blood Glucose BUN***: Blood Urea Nitrogen

Table 3. Correlation Analysis between Blood Osmolality & Age and Gensini & Syntax Score for Group 1

	Age	Osmolality	Gensini
Age			
r	1	0.17	0.05
p		0.06	0.67
N	113	113	71
Osmolality			
r	0.17	1	-0.24****
p	0.06		0.04*
N	113	113	71
Gensini			
r	0.05	-0.24****	1
p	0.67	0.04*	
N	71	71	71
Syntax			
r	0.016	-0.14****	0.57

P*<0.05 statistically significant, r****: Correlation Coefficient

Discussion

The calculated serum osmolality in the group with more than 50% stenosis in the coronary arteries and the group with less than 10% stenosis in the coronary arteries were with in the normal interval, and there was no statistically significant difference ($p = 0.19$). Despite this, the preprandial blood glucose (PBG) value of the group with severe coronary artery stenosis was statistically significantly higher than in the other group ($p = 0.02$). This was thought to be related to stress hyperglycemia. Blood urea nitrogen values were found to be normal, and no significant difference was found.

The sodium values were found to be within the normal interval for both groups and were found to be statistically significantly lower for the group with over 50% stenosis ($p = 0.01$). The gradual reverse regression of sodium value can also be attributed to stress hyperglycemia because each increase in glucose of 100 mg/dl causes a decrease in sodium value of approximately 1.6 mEq/dl [11]. Hypothyroidism may also cause dilutional hyponatremia. Additionally, the significantly higher total cholesterol, LDL and TG values of patients with coronary artery stenosis >50% may have contributed to this situation by creating pseudohyponatremia.

In the study by Korkut and Sevinç (2021) examining the correlation between chronic diseases and death anxiety; the mean age was 43.62 ± 13.27 years, and the death anxiety score was the highest for 51 years old and over (50.13±12.04) [12]. In our study, the mean age in Group 1, which experienced 50+% stenosis, was 58.4 ± 10.8 years, which is similar to the aforementioned mean age in which death anxiety is high.

Wahab et al. (2002) studied 1664 patients who were admitted to the hospital with acute myocardial infarction (a study that did not exclude diabetic patients) for one year. The study showed that hyperglycemia at the time of admission was associated with clinical outcomes with high mortality, especially for high-risk patient groups [13]. Stress hyperglycemia, increased serum catecholamine and cortisol levels, decreased insulin sensitivity, and the associated increased presence of harmful free fatty acids can explain this [14].

While urea is absorbed by passive diffusion in the proximal tubule, its absorption from the distal tubule is mostly related to the absorption of water, occurring under the control of anti-diuretic hormone regulated by angiotensin II [15, 16]. Renal hypoperfusion occurring during acute coronary syndrome may cause an increase in BUN and is more valuable than creatinine and glomerular filtration rate (eGHR). A study by Kirtane et al. (2005) of 9420 people with normal and moderately reduced GFR who applied to the hospital with ACS, demonstrated that high BUN values, which contribute significantly to osmolality, can be used as a mortality factor independent of serum creatinine, creatinine clearance and eGFR [17].

A 10-year study conducted by Funk et al. (2010) including 151,486 people, showed that serum dysnatremia detected during hospitalization of patients admitted to the intensive care unit may be an indicator of poor prognosis regardless of the underlying diseases [18]. Tatlisu et al. (2017) found that hyperosmolality can be an independent indicator in determining the duration of hospitalization and, in the long-term, mortality in a study including 3748 patients who applied to the hospital with ST-elevation myocardial infarction (STEMI) and underwent coronary angiography. Patients were divided into 4 quadrants (Q1, Q2, Q3, Q4) from lowest to highest according to their osmolality values at the time of admission to the hospital; it was observed that the quartile with the highest osmolality (Q4) experienced more cardiogenic shock, acute respiratory failure, ventricular arrhythmia, stent thrombosis, recurrent MI, revascularization, and mortality rate (95%) during the hospitalization. When the 3-year survival of these groups was examined, the complication and mortality rates of Q4 were higher [19]. As a result, high serum osmolality value was determined to negatively affects the prognosis of coronary artery disease.

A six-year study by Kaya et al. (2017) including 509 people examined the success of plasma osmolality in determining mortality for heart failure patients with low ejection fraction (EF) and found that hypoosmolality was an indicator that could be used independently of EF, Brain Natriuretic Peptide (BNP) and functional capacity [20].

Excluding DM patients prevented us from making a comparison, but when we evaluated biochemical indicators, prediabetic patients were included in the study. A study of 315 people by Rasouli et al. (2008) found that there was a significant correlation between the severity of CAD and serum osmolality, especially between glucose and BUN values, but the correlation decreased for diabetic patients [21].

Zhao T et al. (2018) conducted a study to determine the predictive value of PBG in determining the severity of coronary artery disease. They revealed that PBG showed a positive correlation with the Gensini score for non-diabetic patients after applying coronary angiography to 64 people, but they did not find any correlation with the Syntax score [22]. The results of the study are similar to ours. This may be because the significant positive correlation of the Syntax score starts with 50% coronary artery stenosis, while the Gensini score starts with 25% coronary artery stenosis. Considering this, Gensini scoring is a more sensitive scoring system for detecting early atherosclerosis.

Limitations

This study was a single-center study. Diabetes mellitus and kidney failure diseases made the groups more sterile and caused a decrease in the number of cases. In addition, the use of calculated data instead of measured osmolality can be considered as a limitation. Not requesting TSH tests from patients who were to undergo angiography was also accepted as a limitation that prevents the implications of thyroid disorders on the findings.

Conclusion

This study sought an answer to the question of whether serum osmolality can be a risk factor that can be used to detect coronary artery diseases. We found that there was no significant difference between the serum osmolality of the two groups when we excluded diabetes mellitus and severe organ failure for the two groups who underwent coronary angiography and had >50% stenosis and <10% stenosis in the coronary arteries. Since we could not find another study with such broad exclusion criteria in the literature, we think that our study is specific in its field; besides, the importance of osmolality regarding the development of CAD can be discussed more clearly and reliably with multi-center studies with a higher number of cases.

Values such as increased blood sugar, total cholesterol, triglyceride, waist-hip circumference ratio of the group with coronary artery stenosis above 50% suggested the possibility of prediabetes; the previous studies show that in cases where each parameter affecting osmolality is worsened, it poses a risk in terms of cardiovascular diseases, regardless of the underlying cause.

For the non-communicable disease group, it is critical for public health to determine the risk factors for coronary artery disease, and to take measures. It is possible to increase the life quality and expectancy by determining the risk score with an as inclusive approach as possible and taking protective measures for it.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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